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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,021	FRANCIS-LANG ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) *5,7-15 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *N/A* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/05/2009 has been entered.

Claims 2 and 17 are cancelled. Claims 1,3,4,16 and 26 are amended. Claims 1,3-16 and 18-28 are pending. Claims 5, 7-15 and 18-25 are withdrawn. Claims 1,3-4,6, and 16 are under examination in the instant office action.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,3-4,6,16 and 26-28 remain rejected and newly added claims 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has performed a screen in Drosophila for genetic modulators of a phenotype caused by overexpression of Chk1, a gene that modulates what the specification refers to as the CHK pathway. The CHK pathway appears to be generically a term encompassing various cell-cycle checkpoints. The specification teaches that modulators of this global CHK pathway are referred to as PAKs (see page 3, lines 8-10). A specific modulator of the Chk1 overexpression phenotype was identified, PAK1. The art at the time of filing taught a role for Pak1, a chk1 ortholog, in cytoskeletal reorganization andsignaling (see

Sells et al, 1997; Bagrodia et al, 1999). However, the specification and art at the time of filing dail to provide a nexus between PAK1 and the claimed "CHK" pathway.

In the Drosophila screen of the invention, Chk1 was overexpressed in the eye, leading to G2 cell cycle arrest and deterioration of eye morphology. Transposon insertion mutagenesis was used to screen for modulators of the phenotype. Modulators would be considered to act by modulating Chk1 and would be considered to be part of the Chk1 pathway. The chk1 gene, through this method, was found to enhance the phenotype caused by overexpression of chk1 (page 34, line 32). Thus, it appears that insertion of the Tn into the endogenous chk1 gene exacerbated the effect of transgene overexpression of chk1. The fly chk1 gene was found to have 52% amino acid identity with human p21-activated kinase Pak1 (see Genbank NP_002567), also referred to as SEQ ID NO:7 in the instant application. The specification fails to further characterize the transposon insertion into the fly chk1 gene (ortholog of human Pak1) that is reported to enhance the chk1 overexpression phenotype.

The specification teaches that PAK RNAi knockdown resulted in decreased proliferation of MCF7 breast cancer cells (page 38). Thus, decreased PAK resulted in decreased proliferation, whereas overexpression of chk1 in Drosophila resulted in cell cycle arrest. Human PAK overexpression in cells in vitro had no effect on colony growth, however, some transcription factor expression was increased (paragraph bridging pages 38-39).

The specification fails to correlate the overexpression of chk1 in the drosophila eye to in vitro overexpression of PAK in mammalian cell culture. There appears to be inconsistencies in the effects of overexpression of chk1 in the fly, the enhancement of the overexpression phenotype by transposon insertion into the endogenous chk1 gene, and the effects of knockdown and overexpression of the human PAK homolog in cell lines. Without such a correlation, one of skill in the art would not know how to use the claimed invention. More characterization of Pak1 and its relation to the "CHK" pathway is necessary before any use can be determined.

The claims relate to identifying modulators of a "CHK" pathway. It is not defined what constitutes the "CHK" pathway. There are many signaling pathways involved in various cell cycle checkpoints. It is not known if all of these are considered to be part of the CHK pathway and it is not clear if the CHK pathway is intended to refer to a single signaling cascade or all checkpoint signaling pathways as a whole. The specification discusses a single genetic modulator screen and is extrapolating this to methods of screening for agents that affect any component that modulates any cell cycle checkpoint. The specification is not enabling for such broad extrapolation to unknown, unidentified, and uncharacterized signaling pathways and molecules. The regulation, binding partners and pathway directly involving Pak1 was being characterized at the time of filing (see Bagrodia, 1999) and it was not known how Pak1 fit into regulation of cell cycle checkpoints. Thus, it was entirely unpredictable how it fit into the global "CHK" pathway referred to in the specification.

Although transposon insertion into chk1 enhances a phenotype associated with chk1 overexpression in drosophila, the disclosure does not convincingly demonstrate how chk1, or its human ortholog Pak1, acts in the CHK pathway, or whether it acts in the ill-defined CHK pathway. One of skill in the art would recognize that enhancement of a mutant phenotype can occur through divergent pathways. Thus, chk1 expression could give rise to enhancement of said phenotype associated with CHK overexpression through pathways that do not involve members of the CHK signaling pathway. Likewise, if experimentation found that a human Pak1 functions in a similar manner to drosophila chk1, said Pak1 could give rise to enhancement of said phenotype associated with chk1 overexpression through pathways that do not involve members of the CHK signaling pathway.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods of identifying candidate CHK pathway modulating agent, comprising providing an assay system comprising a cell expressing a PAK1 polypeptide or nucleic acid; contacting the assay system with a test agent whereby, but for the presence of the test agent, the system

provides a reference activity; and detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate CHK pathway modulating agent, and Applicant has not enabled said methods because it has not been shown that human Pak1 could be used in the claimed method to predictably identify "CHK pathway" modulating agents.

With respect to using a subject as the assay system, problems related to *in vivo* use of nucleic acids were well known in the art at the time of invention and persist to the present day; see **Opalinska et al.** (Nature Reviews Drug Discovery 2002). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a measurable or therapeutic effect.

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo*; due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of nucleic acids *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the nucleic acid reaching the proper cell

in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of nucleic acid sequences *in vivo* or *in vitro*, such that the nucleic acid provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The instant specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acid modulators for *in vivo* applications. The teaching of the prior art does not provide that guidance. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

Additionally, step b of claim 1 is drawn to contacting the assay system with "a test agent that modulates the expression and/or activity of said Pak1". If an agent is known to modulate PAK1, then nothing is accomplished by the method. The method amount no more than making a correlation between a known PAK1 modulator and the CHK pathway such that one considers it a 'candidate' CHK modulator. Nothing is gained in carrying out the claimed method and additional experimentation would be necessary to determine if the 'candidate' agent is a CHK modulator such that one would know how to use it. Any agent can be considered candidate agent, without any assay, and as set forth above, the specification fails to provide any evidence that a modulator of PAK1 would modulate the CHK pathway.

Applicant's arguments have been fully considered. The aspect of the rejection regarding the breadth of PAKs encompassed by the claims is withdrawn in light of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Utility

Claims 1,3-4,6,16 and 26-28 are rejected are under 35 U.S.C. 101 because the claimed invention lacks patentable utility. Claims 1,3-4,6,16 and 26-28 recite a method for identifying a "candidate" p21 pathway modulator. To satisfy 35 U.S.C. 101, an invention must be "useful", i.e. be specific and substantial. A "specific utility" is *specific* to the subject matter claimed and can provide a well-defined and particular benefit to the public. To be substantial, the invention must be useful to the public as disclosed, not that it may prove useful at some future date after further research (see MPEP 2107). In the instant case, the method is designed to merely identify a "candidate" CHK pathway modulator. Thus, the method fails to have a specific and substantial benefit to the public without further research to determine if the "candidate" modulator is, in fact, a modulator of a CHK pathway. Practicing the recited steps has no immediate benefit to the public. See enablement rejection above.

Claims 1,3-4,6,16 and 26-28 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claim is allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632